False-negative findings in skin cancer and melanoma screening

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Background: Few data are available on the accuracy of visual skin examination by dermatologists as a skin cancer and melanoma screening tool.
Objective: The purpose of this study was to assess the number of false-negative findings in a skin cancer–melanoma screening program.
Methods: We obtained follow-up information regarding 1551 persons with a negative screening result in a skin cancer–melanoma screening program in 1990. Follow-up was established by record linkage with two different population-based registries.
Results: Fifteen persons had new skin cancers. Three of their lesions had been present at the original screening and had probably been missed; 12 were genuinely new. No melanomas were among the missed cases. The calculated sensitivity of the screening was 93.3%, its specificity was 97.8%, its positive predictive value was 54.0%, and its negative predictive value was 99.8%.
Conclusion: Visual examination by dermatologists as a screening tool for skin cancer and melanoma is appropriate.
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Screening for skin cancer and melanoma facilitates early detection and may reduce morbidity and mortality. Visual inspection of the skin by dermatologists constitutes a rapid and inexpensive screening.

The accuracy of visual examination depends on the proportion of true-positive, false-positive, true-negative, and false-negative results:

$$\text{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}$$

$$\text{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}}$$

$$\text{Positive Predictive Value} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}$$

$$\text{Negative Predictive Value} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}}$$

False-negative results may be harmful to the patients screened by causing a false feeling of security that may result in undue delays in diagnosis later. Ideally, therefore, a test detects only diseased persons and detects all of them. The test should be highly sensitive, although a relatively high proportion of false-positive results are acceptable; this especially relates to skin cancer, because diagnosis and treatment of benign skin lesions is easy and inexpensive.

The accuracy of skin cancer–melanoma screening has not been studied extensively. Some studies have examined the positive predictive value of skin cancer–melanoma screening by assessing the true-positive and false-positive results.[1-3] False-negative screening results derived from follow-up of persons with negative findings have never been reported. Assessment of the false-negative rate necessitates follow-up of all persons with negative screening results for several years. We studied the occurrence of skin malignancies in 1551 persons with negative screening results during 42-months of follow-up.

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Table I. Persons with new skin malignancies during follow-up

Patient No.	Diagnosis	Site	Presumptive diagnosis at screening	Time interval (mo)
1	BCC	Back	NA	36
2	BCC	Nose	NA	16
3	SCC	Lip	NA	35
4	SCC	Wrist	Seborrheic wart	32
5	BCC	Forehead	Actinic keratosis	41
6	BCC	Chin	NA	15
7	BCC	Nose	NA	5
8	BCC	Groin	NA	17
9	BCC	Shoulder	NA	22
10	BCC	Head	NA	2
11	BCC	Chest	NA	40
12	BCC	Back	Common nevus	9
13	BCC (4)*	Face	NA	11-38
14	Melanoma	Leg	NA	30
15	Melanoma	Knee	NA	33

BCC, Basal cell carcinoma; NA, not applicable; *SCC*, squamous cell carcinoma.
*Four different lesions.

METHODS

In June 1990 six skin cancer–melanoma screening programs were conducted in the region of Arnhem. The area includes approximately 650,000 persons. The area has seven dermatologists, all of whom participated in the study. Practical considerations and screening results have been published previously.[3,4]

All attending persons were asked to grant permission for evaluation of new skin cancers. Malignancies that were not shown on the participants or not recognized as such by the physicians during the screenings, but recorded during follow-up, were indicated as new skin cancers. Follow-up of persons who had given permission was established by computerized record linkage with two different population-based registries: the Regional Cancer Registry of the Comprehensive Cancer Center Integraal Kankercentrum Oost (IKO), and Pathologisch Anatomisch Landelijk Geautomatiseerd Archief (PALGA), the Dutch national data base of pathology records.

The records of the participants who had given informed consent for follow-up were linked with the skin cancer records in both registries for cases diagnosed from June 1990 to December 1993. In the first stage of the record linkage, records were matched by using as identifiers date of birth, sex, and family name. In addition, to detect missed matches because of incomplete or inaccurate identifiers, various combinations of parts of the identifiers were used for linkage. The latter procedure was carried out only in the linkage with the regional cancer registry. In the second stage of the record linkage any false-positive matches were distinguished by a check of other identifiers such as initials, maiden name, and residence. This protocol for record linkage has a high sensitivity and a low number of false-negative matches.[5]

RESULTS

A total of 1961 persons attended the screenings. There were 198 referrals for presumed skin cancer ($n = 87$) or distinct precursor lesions ($n = 111$). Referral was not made for less marked or borderline precursor states. Clinical evaluation disclosed 51 malignancies in 47 persons screened: five melanomas, one lentigo maligna, 40 basal cell carcinomas, one squamous cell carcinoma, and four cases of Bowen's disease. Additionally, one presumed dysplastic nevus turned out to be a melanoma. All malignancies were histopathologically confirmed. In addition, several clinically obvious basal cell carcinomas diagnosed at one of the clinics were treated with cryosurgery without pathologic assessment. These cases, however, were not included in the study. Compliance with referral among persons with suspected skin cancer was nearly complete (93%).

The follow-up efforts concentrated on the 1763

attendees with negative screening results. Of these, 1551 (88%) had given written consent to obtain follow-up information. Fifteen persons proved to have skin cancer diagnosed during the 42 months of follow-up. Of these, 14 were linked with both registries. One match was reported by the regional cancer registry only. Table I details these cases. One patient had four basal cell carcinomas during follow-up. The other cases represent single diagnoses.

Twelve instances were related to frankly new skin cancers, not present or discovered during the screens. Three patients had skin cancer diagnosed at sites that were thought to be normal or benign at the original screening. One patient had a basal cell carcinoma on his back after 9 months of follow-up. This patient attended the screening for a general skin check. The records mentioned several common nevi on the back. The basal cell carcinoma was probably missed at initial presentation. The second patient had a squamous cell carcinoma on his wrist, recorded as a seborrheic keratosis 32 months previously. The third had a basal cell carcinoma on the forehead. The original diagnosis at screening 41 months earlier was actinic keratosis.

Three false-negative screening results were found, as compared with 1548 true-negative results, among the 1551 persons available for follow-up. However, to assess the exact rate of true-negative results, the number of persons with negative screens who did not consent to follow-up ($n = 212$) must be included. The calculated number of false-negative results in the total group of negative screening findings is $1763 \div 1551 \times 3 = 3.4$. Thus the number of true-negative results becomes 1759.6. True-positive results were obtained in 47 of the 87 cases with presumed malignancy. Thus the number of false-positive results is 40. From these data the sensitivity of our screening exercise was calculated as $47 \div 50.4 = 0.933$ (93.3%). The specificity was $1759.6 \div 1799.6 = 0.978$ (97.8%), the positive predictive value was $47 \div 87 = 0.54$ (54.0%), and the negative predictive value was $1759.6 \div 1763 = 0.998$ (99.8%). The persons who were referred for distinct precursor lesions ($n = 111$) are difficult to categorize. In a strict sense they have to be regarded as having negative screening results. Yet they were referred and followed up as those with positive screening results. For that reason they have not been considered in the assessment of sensitivity, specificity, and predictive values.

The prevalence of skin cancer in this group of screened persons was 51 of 1961, or 2.6%. In these 51 persons, 55 skin malignancies were detected. The cases of skin cancer included 47 true-positive results, three false-negative results, and one case of melanoma initially classified as a dysplastic nevus. Actually the true prevalence rate was slightly higher because several basal cell carcinomas had been treated without pathologic confirmation; these tumors were not included in the study.

DISCUSSION

Screening for skin cancer and melanoma, although promising, remains a debatable issue.[6-10] One important question about the validity and accuracy of the screening test studied, that is, visual examination of skin lesions by dermatologists, is its sensitivity, specificity, and predictive value.

Most skin cancers diagnosed during follow-up in this study in persons with negative screening findings were new tumors. Twelve of 15 persons had lesions that were not present or that had not been found during the screening. Only three lesions actually proved to be false-negative lesions, a rate of only 0.2% of the entire group of 1551 persons with negative screening findings, followed up for 42 months.

These findings are encouraging. Visual examination of skin lesions by dermatologists appears to be a reliable screening tool. Koh et al.[2] estimated the sensitivity of skin examination by dermatologists to be 97% for melanoma, 94% for basal cell carcinoma, and 89% for squamous cell carcinoma. These estimates, however, were not generated from their own screening results. Persons with negative screening results were not followed. The authors equated the false-negative rates with the population incidence rates to produce an estimated sensitivity. Our sample size is not large enough to generate sensitivity values for skin cancer subtypes. The overall sensitivity rate was calculated as 93.3%.

Our results provide the first sensitivity estimates for a visual examination performed by dermatologists in a skin cancer–melanoma screening setting. The sensitivity of 93.3% seems to compare favorably with sensitivities that have been documented for other cancer screening tests, such as fecal occult blood test for colon carcinoma (69%), mammography for breast cancer (75%), and the Pap smear for cervical cancer (78%).[2] However, comparison with other screening settings is precarious. Among other reasons, instituted screening programs are a continuous process and attract incident cases. Our screen-

ing effort was a pilot study in an area without previous screening for skin cancer and melanoma. Therefore the yield of this screening consists of prevalent cases.

We included any possible skin cancer in the follow-up period, because this method produces the most conservative estimate. We traced three persons in whom skin cancer developed 9, 32, and 41 months after voluntary screening. One had a back lesion, initially diagnosed as a nevocellular nevus, that turned out to be a basal cell carcinoma after 9 months. The other false-negative screen results, one squamous cell carcinoma and one basal cell carcinoma, showed a long delay of 32 and 41 months, respectively. It is possible that these two tumors were borderline lesions at the time of presentation during screening and were difficult or impossible to recognize even by an experienced dermatologist. On the other hand, a more thorough search for false-negative results and/or a longer follow-up period might have disclosed additional missed cases.

We did not include in the number of false-negative screening results the person with a melanoma that was misdiagnosed as an atypical nevus. The aim of our screening was to detect skin cancer and important precursor lesions. Persons with atypical nevi of high suspicion were given a referral letter to their general physician. In this group, although the presumed diagnosis at screening may be incorrect, a suspect lesion will still be properly managed, thereby fulfilling the critical function of the screening. Because the group of 111 persons with referrals for precursor lesions is difficult to classify properly, we decided to exclude these attendees from analysis. If these persons are regarded as having negative screen results and if the one melanoma detected in this category is regarded as a false-negative finding, then the sensitivity of our screening would drop from 93.3% to 91.3%.

Other factors may have influenced the low score of false-negative findings. Persons may have died during the observation period with or from undetected malignancies. Second, within the Arnhem region it is estimated that migration to other municipalities occurs at a rate of 4% to 5% each year. Many persons, however, migrate to other municipalities within the same area. These do not escape detection by the Regional Cancer Registry. Even if migration occurs outside the region, the national pathology data base (PALGA) would be able to trace such instances.

The potential underreporting of melanoma and nonmelanoma skin cancer by pathology laboratories and cancer registries may be debatable.[1, 11] Completeness of reporting skin malignancies in the area under investigation is estimated at around 93%.[12] We used two different registries for record linkage. This will certainly have reduced the rate of underreporting.

The proportion of referrals in this campaign was 10.1% (198 of 1961). This rate is lower than those reported in some American studies.[1, 2] One probable reason for the discrepancy is the selective referral policy for precursor lesions in our series. To preclude unwarranted treatment, only distinct precursor lesions were referred. Persons with minimal evidence of actinic keratoses, dysplastic nevi, or other intermediate or borderline lesions were not referred.

Dermatologists are able to detect melanomas and other skin cancers adequately. The low false-negative rate and the favorable sensitivity of visual inspection of the skin as a screening tool reported in this study may lose much of their value when other disciplines or paramedical personnel are employed during screening. The relative lack of proper recognition of melanoma by nondermatologists is worrisome.[13-15] It has been argued whether screening procedures for skin cancer and melanoma should be performed by general physicians, nurse clinicians, or paraprofessionals. Specifically trained dermatology nurses have been employed for (pre)screening, with fair agreement rates.[1] In general, however, evidence favors screening by dermatologists only.

REFERENCES

1. Bolognia JL, Berwick M, Fine JA. Complete follow-up and evaluation of a skin cancer screening in Connecticut. J Am Acad Dermatol 1990;23:1098-106.
2. Koh HK, Caruso A, Gage I, et al. Evaluation of melanoma/skin cancer screening in Massachusetts. Cancer 1990; 65:375-9.
3. Rampen FHJ, van Huystee BEWL, Kiemeney LALM. Melanoma/skin cancer screening clinics: experiences in The Netherlands. J Am Acad Dermatol 1991;25:776-7.
4. Rampen FHJ, van Huystee BEWL, Kiemeney LALM. Practical considerations of melanoma/skin cancer screening clinics. Dermatology 1992;184:190-3.
5. van den Brandt PA, Schouten LJ, Goldbohm RA, et al. Development of a record linkage procedure for use in the Dutch cancer registry for epidemiologic research. Int J Epidemiol 1990;19:553-8.
6. Koh HK, Lew RA, Prout MN. Screening for melanoma/skin cancer: theoretic and practical considerations. J Am Acad Dermatol 1989;20:159-72.
7. Koh HK, Miller DR, Geller AC, et al. Screening for melanoma and other skin cancers. Clin Dermatol 1992;10:97-103.

8. Rampen FHJ, Neumann HAM, Kiemeney LALM. Fundamentals of skin cancer/melanoma screening campaigns. Clin Exp Dermatol 1992;17:307-12.
9. McDonald CJ. Status of screening for skin cancer. Cancer 1993;72:1066-70.
10. Elwood JM. Screening for melanoma and options for its evaluation. J Med Screening 1994;1:22-38.
11. Koh HK, Clapp RW, Barnett JM, et al. Systematic underreporting of cutaneous malignant melanoma in Massachusetts. J AM ACAD DERMATOL 1991;24:545-50.
12. Schouten LJ, Straatman H, Kiemeney LALM, et al. The capture-recapture method for estimation of cancer registry completeness: a useful tool? Int J Epidemiol 1994;23:1111-5.
13. Cassileth BR, Clark WH Jr, Lusk EJ, et al. How well do physicians recognize melanoma and other problem lesions? J AM ACAD DERMATOL 1986;14:555-60.
14. Rampen FHJ, Rümke P. Referral pattern and accuracy of clinical diagnosis of cutaneous melanoma. Acta Derm Venereol (Stockh) 1988;68:61-4.
15. Williams HC, Smith D, du Vivier A. Melanoma: differences observed by general surgeons and dermatologists. Int J Dermatol 1991;30:257-61.